PORTAL HYPERTENSION IN THE RAT.

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ALTHOUGH portal hypertension is now a well-recognised clinical syndrome, attempts to reproduce the condition in animals by simple mechanical obstruction of the portal vein or its tributaries have so far been unsuccessful. It has often been shown that complete ligature of the portal vein in dogs, cats and rats is a fatal procedure (Elman and Cole, 1934; Boyce, Lampert and McFetridge, 1935; Menon, 1938), although Milnes and Child (1949) have shown that Rhesus monkeys will survive complete occlusion of the portal vein in one stage.

Warthin (1910) attempted to produce splenomegaly in rabbits and dogs by ligature of the splenic vein, but without success. Jäger (1931) constricted the portal vein of the dog and also did a reversed Eck fistula followed by ligation of the vein, but there was little splenic enlargement although histological changes were found in the spleen. Menon (1938) attempted partial occlusion of the portal vein in rabbits and rats by various techniques, but the results were somewhat inconstant although some rats showed splenic enlargement up to about twice the normal size. Rousselot and Thompson (1939) produced a condition resembling congestive splenomegaly with raised portal venous pressure in the dog by repeated injection of silica particles into the splenic vein, but this cannot be classified as a simple mechanical obstruction. Volwiler, Grindlay and Bollman (1950) were unable to produce a significant rise of portal venous pressure in the dog by various constrictions of the portal vein, although there was some rise after constriction of the intrathoracic inferior vena cava. There was no significant splenomegaly in these dogs.

The repeated failure to reproduce the human syndrome in a variety of experimental animals is unexplained, but most previous workers have been concerned primarily with splenic changes, and it was felt that a study of the effects of a sudden subtotal obstruction of the portal vein in the rat on portal venous pressure, the development of collateral circulation and the size of the spleen might provide some clue to the apparent paradox.

The effect of splenectomy on the portal venous pressure of an animal with portal hypertension would be worth investigating, as the operation is still performed on patients with Banti's syndrome with the object of reducing the portal venous pressure by cutting off some 20 per cent of the arterial inflow into the portal system.

EXPERIMENTAL.

Constriction of the portal vein.

Young female rats of the Wistar strain (weight 150–220 g.) were used. The portal vein was constricted by a modification of the method described by Whitaker

(1946). The animal was anaesthetized with ether and the duodenum was identified and withdrawn through a midline incision to expose the portal vein. A ligature was placed around the vein above the small pyloric vein, which is the last tributary received by the main trunk of the portal vein. A piece of wire 1/40 in. diameter was then placed alongside the vein and the ligature was tied tightly over it. The wire was then withdrawn and the abdomen closed in two layers. In a few animals a second ligature was tied loosely around the vein and the ends drawn out through the skin as described by Whitaker, to be pulled tight three days later, but this second ligature was of doubtful efficacy. About 50 per cent of the animals died within a few hours of operation, but the results of less severe constrictions were disappointing.

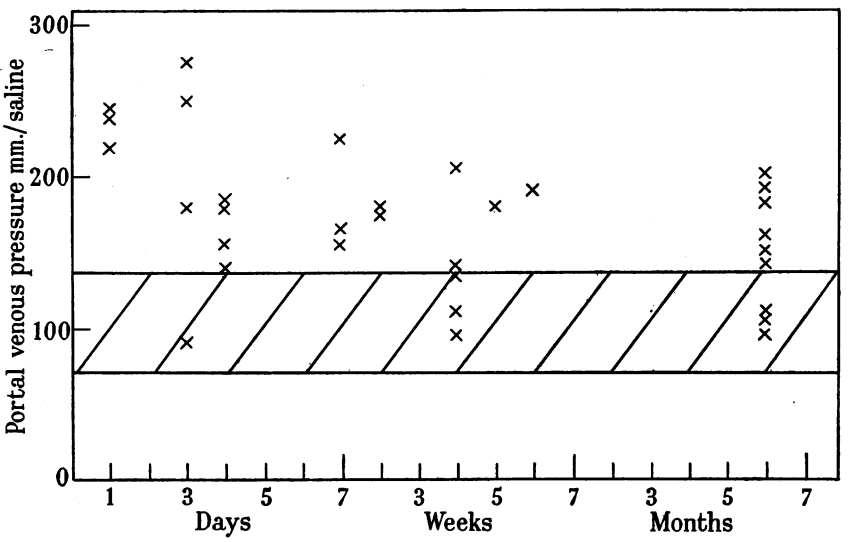


FIG. 1.—Readings of the portal venous pressure after constriction of the portal vein. The shaded area indicates the range of normal values.

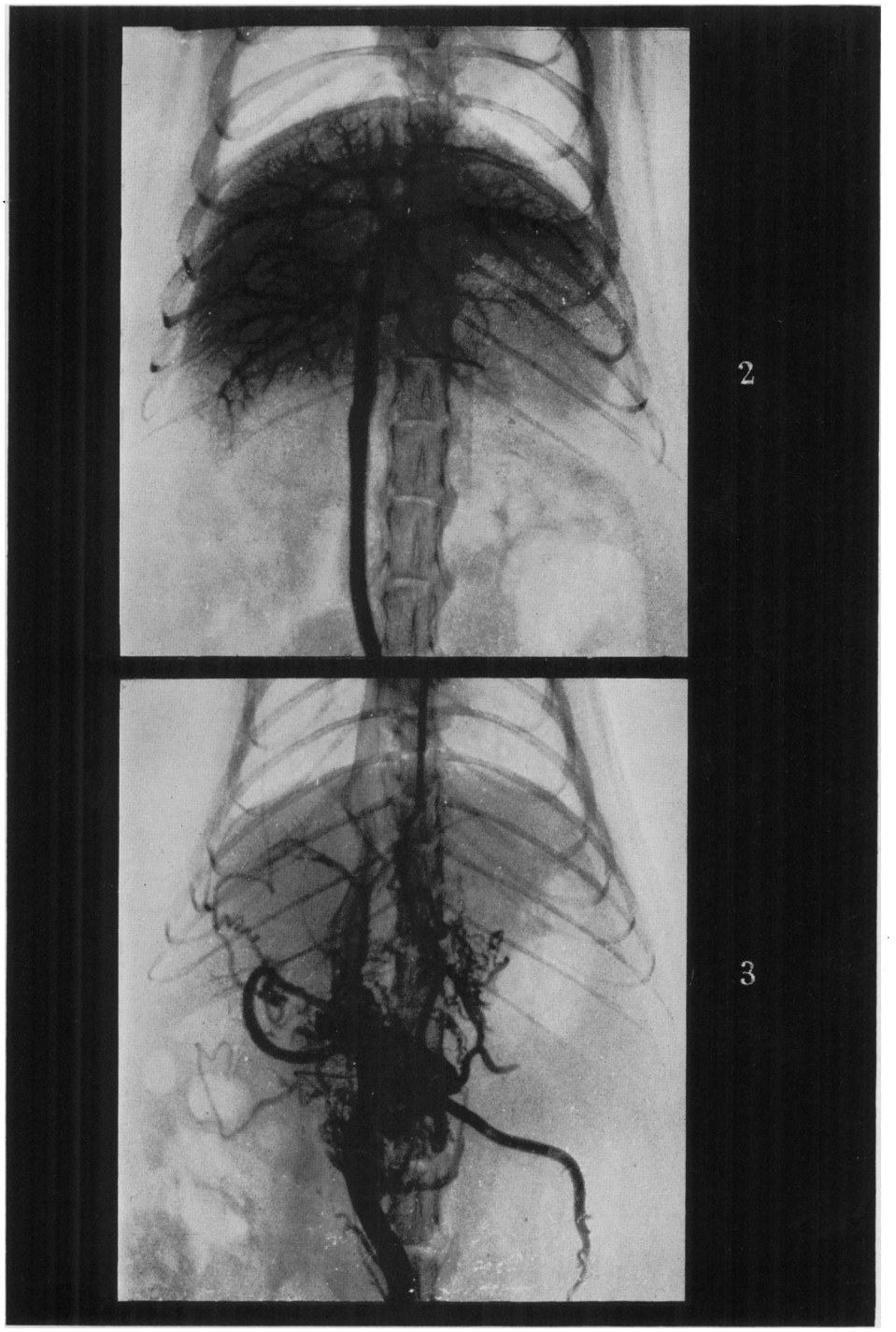
The effect on portal venous pressure.

The pressures were measured with a 20 gauge serum needle and a saline manometer. The needle was inserted about 2 cm. into the distal end of the superior mesenteric vein near the caecum and the column of fluid in the manometer was allowed to fall until a steady level was attained. Readings of the portal venous pressure were obtained in 24 normal rats of the same age, sex and strain as those subjected to constriction of the portal vein, and in these animals all values fell within the range 70–140 mm. saline. Pressures were also estimated in 35

DESCRIPTION OF PLATES.

FIG. 2.—Single frame from the angiogram of a normal living rat taken 3 sec. after the first appearance of contrast medium at the porta hepatis.

FIG. 3.—Single frame from the angiogram of a rat subjected to constriction of the portal vein 2 weeks previously, taken 3 sec. after the first appearance of contrast medium at the porta hepatis. Nearly all the portal venous blood is diverted away from the liver into collateral vessels (paraoesophageal, retroperitoneal and vessels to the anterior abdominal wall).



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animals at varying intervals of time after constriction of the portal vein and the results are shown in Fig. 1. In three animals the pressure was measured immediately after tying the ligature and values of 720, 470 and 380 mm. saline were obtained. Within 24 hours the pressure had fallen to the 200–270 range. By the end of the first week pressures varied between normal and twice normal, but thereafter showed no further tendency to fall; even after six months pressures up to twice normal were recorded.

The development of collateral circulation.

The collateral circulation was studied in the living animal by the technique of rapid serial angiography which has been described more fully elsewhere (Daniel and Prichard, 1951). A small quantity of thorotrast was injected into a branch of the superior mesenteric vein of the anaesthetized animal, and the passage of the column of contrast medium through the liver and collateral vessels was recorded by serial radiographs taken at the rate of two per second. The collateral circulation was visualised in this way in eight animals which had been subjected to constriction of the portal vein one to six weeks previously (Fig. 2 and 3). In three of them this investigation was supplemented by the post-mortem injection of a suspension of bismuth carbonate into the superior mesenteric vein followed by stereoscopic radiography with the organs *in situ* and finally by dissection of the injected vessels.

It was apparent that the collateral circulation was fully formed by the end of the first week after operation, as angiograms taken after longer intervals did not suggest that collateral vessels had become either larger or more numerous. In all animals the portal vein and its tributaries were tortuous and distended and an extensive collateral circulation was always present. The anatomy of the collateral vessels bore some resemblance to those found after obstruction of the portal vein in man. The channels most frequently utilised were as follows:

1. Paraoesophageal vessels ran upwards to join the azygos or pulmonary veins. These were subserosal; submucous oesophageal varices were not seen.
2. Retroperitoneal vessels anastomosed either with the inferior vena cava or the left renal vein.
3. Collateral vessels to the anterior abdominal wall formed at points at which the omentum became adherent to the parietal peritoneum.
4. Sometimes bloodflow in the inferior mesenteric vein was reversed, and blood escaped by way of anastomoses with the internal or common iliac veins.

The effect on liver and spleen.

Ten rats were subjected to constriction of the portal vein, and twelve others of the same age and sex were run concurrently as controls. At the end of six months all animals were sacrificed. The livers and spleens were excised and placed in a solution of normal saline. Within 90 minutes of excision they were mopped with filter paper and weighed. The weights are shown in Table I. Weights are expressed in mg. per 100 g. body weight, as Hatai (1913) has shown that the relationship between hepatic or splenic weight and body weight is approximately linear in Wistar rats of more than 140 g. The mean weight of the normal spleen was found to be 276 mg./100 g., which is almost identical with the figures given for the Wistar rat by Hatai (1913) and by Jackson (1915). Although the con-

striction appeared to have been ineffective in three of the rats (Nos. 4, 5 and 6), the mean weight of the liver was significantly less and that of the spleen significantly greater in the test group than in the controls. Further observations on splenic weights after constriction of the portal vein have been made during the course of other experiments and it has been found that the spleen is almost invariably significantly enlarged, but in no case did the splenic weight exceed 750 mg./100 g.

TABLE I.—*Weight of Liver and Spleen in mg./100 g. after Constriction of the Portal Vein.*

Rat No.	Spleen weight.	Liver weight.
1	401	3200
2	370	3650
3	378	3020
4	275	4000
5	378	4140
6	227	3870
7	400	3200
8	285	3100
9	308	3340
10	370	3780
Mean	339	3530
Mean of 12 normals	276	3840
S.E. of difference	22.6	139.5

The effect of splenectomy.

Sixty-six rats (56 female and 10 male) were subjected to constriction of the portal vein as already described. Those which survived the operation were left for one month and then subjected to a second laparotomy, at which the portal venous pressure was measured and haemostasis then secured with oxycel gauze. Any animal with a portal venous pressure of less than 130 mm. saline was

TABLE II.—*Portal Venous Pressures in mm. Saline Before and After Splenectomy and in Control Rats not Subjected to Splenectomy.*

Splenectomy.			No splenectomy.		
Rat.	Initial pressure.	Final pressure.	Rat.	Initial pressure.	Final pressure.
1	160	165	1	165	135
2	185	170	2	150	175
3	170	170	3	140	130
4	180	170	4	150	130
5	150	135	5	130	155
6	160	180	6	180	165
7	180	205	7	135	180
8	130	200	8	200	165
9	170	210	9	195	165
10	165	160	10	195	165
11	190	150			
Mean pressure change	+ 8				—7

discarded. Of those with pressures greater than this, alternate rats were subjected to splenectomy. The animals were then allowed to recover and kept for a further month. At the end of this time the abdomen was again opened, a final reading of the portal venous pressure was made and all animals were sacrificed.

Splenectomy did not lead to any sustained fall in portal venous pressure, and there was no consistent change in pressure during the second month after constriction of the portal vein in either splenectomised animals or controls (Table II).

DISCUSSION.

These experiments show that many of the features of portal hypertension in man can be reproduced by simple mechanical constriction of the portal vein in the rat. The difference between the two species is one of degree rather than one of kind. A sustained rise in portal venous pressure up to 200 mm. saline may be achieved in the rat, whereas in the human subject with portal vein obstruction it is usual to find pressures of 200–400 mm. saline (Milnes Walker, 1950). Similarly the splenic enlargement produced in the rat is significant, but not comparable in degree to that often found in man. The species difference is probably due to the facility with which collateral circulation develops in the rat. These studies of the portal venous pressure after constriction of the vein show that the operation results in an immediate rise in pressure, followed by a rapid fall within 24 hours and a slower fall during the next week. The fact that the collateral circulation appears to be fully developed by the end of the first week suggests that this fall in pressure is due to the rapid formation of collateral vessels. In the rat it seems that a portal venous pressure of more than about 250 mm. saline cannot be sustained for long, since at this level fresh collaterals will form rapidly, so that the outflow from the portal system is facilitated, and the portal venous pressure will fall to a level which is insufficient to stimulate the development of fresh collaterals. In man a greater difference between portal and systemic venous pressures is probably required before a significant collateral circulation will develop.

Splenectomy was first advocated in cases of Banti's syndrome by Banti himself (1898) in the belief that the disease had its origin in the spleen. It is now believed that in most if not all of these patients the primary cause of the syndrome is a raised portal venous pressure due to some mechanical obstruction of the portal or splenic vein (Whipple, 1945). It has nevertheless been argued that removal of the spleen will diminish the inflow of arterial blood into the portal system by about 20 per cent and thus reduce the portal venous pressure (McNee, 1932). This argument is a theoretical one, and there is no clinical or experimental evidence that removal of the spleen will in fact produce a sustained fall in portal venous pressure. It is obviously difficult to obtain this information in the human subject, but in rats with portal hypertension produced by subtotal constriction of the portal vein splenectomy did not lead to any sustained fall in portal venous pressure.

SUMMARY.

The effects of a subtotal constriction of the portal vein of the rat have been studied.

The immediate rise of portal venous pressure produced by constriction of the vein is followed by a rapid fall, so that after a week pressures vary between normal and twice normal and thereafter there is no further fall.

An extensive collateral circulation resembling anatomically that found in the human subject is fully formed one week after constriction of the vein. There is a slight but significant reduction in the size of the liver and increase in the size of the spleen.

It is concluded that most of the features of portal hypertension in man can be reproduced in the rat by mechanical constriction of the portal vein. The difference is one of degree, and is apparently due to the greater facility with which collateral vessels develop in the rat.

Splenectomy did not lead to any sustained fall in portal venous pressure in these animals.

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